End of Result Set

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L8: Entry 14 of 14 File: USPT Nov 19, 1996

US-PAT-NO: 5576016
DOCUMENT-IDENTIFIER: US 5576016 A

TITLE: Solid fat nanoemulsions as drug delivery vehicles

DATE-ISSUED: November 19, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Amselem; Shimon	Rehovot			IL
Friedman; Doron	Carmei Yosef			IL

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Pharmos Corporation	New York	NY			02

APPL-NO: 08/ 063613 [PALM]
DATE FILED: May 18, 1993

INT-CL: [06] A61 K 9/127, A61 K 9/16

US-CL-ISSUED: 424/450; 424/489, 424/490, 424/502, 428/402.2
US-CL-CURRENT: 424/450; 424/489, 424/490, 424/502, 428/402.2

FIELD-OF-SEARCH: 424/450, 424/489, 424/490, 424/497, 424/45, 424/427, 424/502, 514/937-943, 428/402.2

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	5023271	June 1991	Vigne	514/458
☐	5171737	December 1992	Weiner	514/3
☐	5188837	February 1993	Domb	424/450
☐	5284663	February 1994	Speaker	424/489
☐	5302401	April 1994	Livensidge	424/501
☐	5306508	April 1994	Kossovsky	424/493
☐	5308624	May 1994	Maincent	424/427

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
0315079	October 1989	EP	
0506197	September 1992	EP	
WO91/07171	May 1991	WO	

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Methods of Biochemical Analysis, vol. 33, D. Glick, editor, J. Wiley & Sons, N.Y., 1988, "Liposomes: Preparation, Characterization, and Preservation", Dov Lichtenberg and Yechezkel Barenholz.
Journal of Pharmaceutical Sciences, vol. 79, No. 12, Dec. 1990, "Optimization and Upscaling of Doxorubicin-Containing Liposomes for Clinical Use", S. Amselem, A. Gabizon and Y. Barenholz.
CRC Press, Inc., 1993, Liposome Technology, 2nd Ed., edited by G. Gregoriadis, Ph.D., vol. 1, Chapter 3, p. 49, "Liposome Peparation Using High-Pressure Homogenizers", Martin M. Brandl, Dieter Bachmann, Markus Drechsler, and Kurt H. Bauer.
Elsevier Science Publishers B.V. (Biomedical Division), 1986, Laboratory Techniques in Biochemistry and Molecular Biology, vol. 3, part 2, edited by R. H. Burdon and P. H. van Knippenberg, "Techniques of Lipidology--Isolation, Analysis and Identification of Lipids", 2nd revision edition, Moris Kates.

ART-UNIT: 152

PRIMARY-EXAMINER: Kishore; Gollamudi S.

ABSTRACT:

The present invention provides pharmaceutical compositions comprising nanoemulsions of particles comprising a lipid core which is in a solid or liquid crystalline phase at 25.degree. C, stabilized by at least one phospholipid envelope, for the parenteral, oral, intranasal, rectal, or topical delivery of both fat-soluble and water-soluble drugs. Particles have a mean diameter in the range of 10 to 250 nm. A wide variety of drugs and oxygen transporting perfluorocarbons may be encapsulated in the particles. In addition to drug delivery vehicles, the invention provides oxygen transporting blood substitutes, and nanoemulsions for extracorporeal maintenance of tissues prior to transplantation.

54 Claims, 3 Drawing figures

☐ Generate Collection

L8: Entry 11 of 14 File: USPT Jul 25, 2000

US-PAT-NO: 6093391
DOCUMENT-IDENTIFIER: US 6093391 A

TITLE: Peptide copolymer compositions

DATE-ISSUED: July 25, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kabanov; Alexander V.	Omaha	NE		
Alakhov; Valery Y.	Quebec			CA

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Supratek Pharma, Inc.	Montreal			CA	03

APPL-NO: 09/ 031279 [PALM]
DATE FILED: February 27, 1998

PARENT-CASE:
This application is a continuation-in-part of U.S. application Ser. No. 08/478,979, filed Jun. 7, 1995, and a continuation-in-part of U.S. application Ser. No. 08/951,079, filed Oct. 15, 1997, U.S. Pat. No. 5,840,319 which is a divisional of U.S. application Ser. No. 08/478,978 filed Jun. 7, 1995, as U.S. Pat. No. 5,817,321, which is a continuation-in-part of Ser. No. 08/374,406, filed Jan. 17, 1995, abandoned, which in turn is a continuation of U.S. application Ser. No. 07/957,998, filed Oct. 8, 1992 abandoned.

INT-CL: [07] A61 K 45/08, A61 K 31/74, A61 K 38/28

US-CL-ISSUED: 424/85.1; 424/94.3, 424/182.1, 424/78.18, 514/3, 514/723
US-CL-CURRENT: 424/85.1; 424/182.1, 424/78.18, 424/94.3, 514/3, 514/723

FIELD-OF-SEARCH: 424/85.1, 424/94.3, 424/182.1, 424/78.18, 424/78.31, 424/78.35, 514/3, 514/723, 514/727, 514/772.3

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4027013	May 1977	Bick et al.	
☐	4106474	August 1978	Hunter et al.	
☐	4188373	February 1980	Krezanoski	
☐	4337760	July 1982	Rubin	
☐	4474752	October 1984	Haslam et al.	
☐	4481195	November 1984	Rubin	

☐	4485457	November 1984	Balaska et al.	
☐	4609546	September 1986	Hiratani	
☐	4740498	April 1988	Hirao et al.	
☐	4772466	September 1988	Alison et al.	
☐	4801452	January 1989	Hunter et al.	
☐	4837014	June 1989	Hunter et al.	
☐	4865835	September 1989	Begent	
☐	4873083	October 1989	Hunter et al.	
☐	4879109	November 1989	Hunter	
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☐	4937070	June 1990	Hunter	
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☐	5028599	July 1991	Hunter	
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☐	5039527	August 1991	Tabibi et al.	
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☐	5089260	February 1992	Hunter et al.	
☐	5114708	May 1992	Hunter et al.	
☐	5143731	September 1992	Viegas et al.	
☐	5152979	October 1992	Hunter	
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☐	5412072	May 1995	Sakurai et al.	
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☐	5449513	September 1995	Yokoyama et al.	

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☐	5470568	November 1995	Lee	
☐	5488034	January 1996	McGregor et al.	
☐	5494660	February 1996	Hunter et al.	
☐	5523492	June 1996	Emanuele et al.	
☐	5554372	September 1996	Hunter	
☐	5567859	October 1996	Emanuele et al.	
☐	5591715	January 1997	Coon et al.	
☐	5622649	April 1997	Hunter et al.	
☐	5648071	July 1997	Hunter et al.	
☐	5656611	August 1997	Kabanov et al.	
☐	5674911	October 1997	Emanuele et al.	
☐	5691387	November 1997	Emanuele et al.	
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☐	5776891	July 1998	Coon et al.	
☐	5817321	October 1998	Alakhov et al.	
☐	5840319	November 1998	Alakhov et al.	
☐	5885590	March 1999	Hunter	424/280.1

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FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
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0 219 922	April 1987	EP	
WO 86/07539	December 1986	WO	
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WO 88/06038	August 1988	WO	
WO89/00812	February 1989	WO	
WO 91/16058	October 1991	WO	
WO 92/00101	January 1992	WO	
WO 92/16484	October 1992	WO	
wo94/08564	April 1994	WO	
WO95/03829	February 1995	WO	
WO96/00801	July 1996	WO	
WO96/40056	December 1996	WO	
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ART-UNIT: 165

PRIMARY-EXAMINER: Wortman; Donna C.

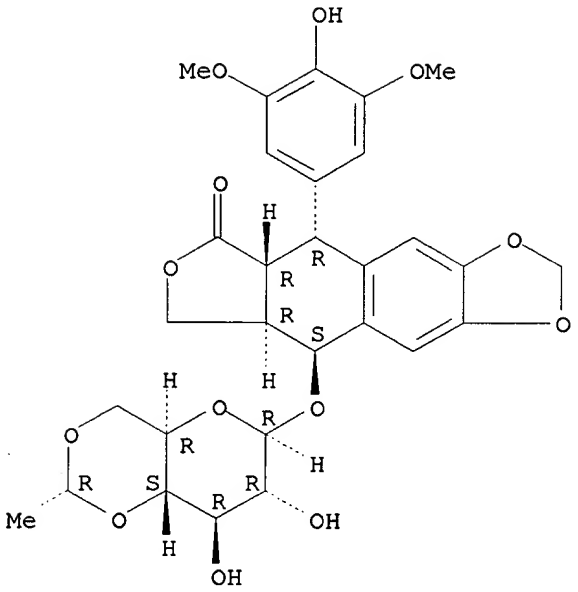
ABSTRACT:

Compositions of peptides and block copolymers and methods of treatment using the same. The compositions enhance the activity of peptide-based and related biological agents, and reduce adverse side effects.

27 Claims, 0 Drawing figures

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 33419-42-0 REGISTRY
CN Furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-one, 9-[[4,6-O-(1R)-ethylidene-.beta.-D-glucopyranosyl]oxy]-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-, (5R,5aR,8aR,9S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Epipodophyllotoxin, 4'-demethyl-, 4,6-O-ethylidene-.beta.-D-glucopyranoside (8CI)
CN Furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-one, 9-[(4,6-O-ethylidene-.beta.-D-glucopyranosyl)oxy]-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-, [5R-[5.alpha.,5a.beta.,8a.alpha.,9.beta.(R*)]]-
CN Pyrano[3,2-d]-1,3-dioxin, furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-one deriv.
OTHER NAMES:
CN (-)-Etoposide
CN 4'-Demethyl-1-O-[4,6-O-(ethylidene)-.beta.-D-glucopyranosyl]epipodophyllotoxin
CN 4'-Demethylepipodophyllotoxin 9-(4,6-O-ethylidene-.beta.-D-glucopyranoside)
CN 4'-Demethylepipodophyllotoxin ethylidene-.beta.-D-glucoside
CN **Etoposide**
CN Lastet
CN NSC 141540
CN trans-Etoposide
CN VePesid
CN VP 16
CN VP 16 (pharmaceutical)
CN VP 16-123
CN VP 16-213
CN Zuyeyidal
FS STEREOSEARCH
DR 121471-01-0, 51854-34-3, 136598-18-0, 76576-58-4, 35317-32-9, 201594-04-9
MF C29 H32 O13
CI COM
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGPAT, DRUGU, EMBASE, HSDB*, IFICDB, IFIUDB, IMSDIRECTORY, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PHAR, PROMT, RTECS*, SYNTHLINE, TOXLINE, TOXLIT, ULIDAT, USAN, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry. Rotation (-).

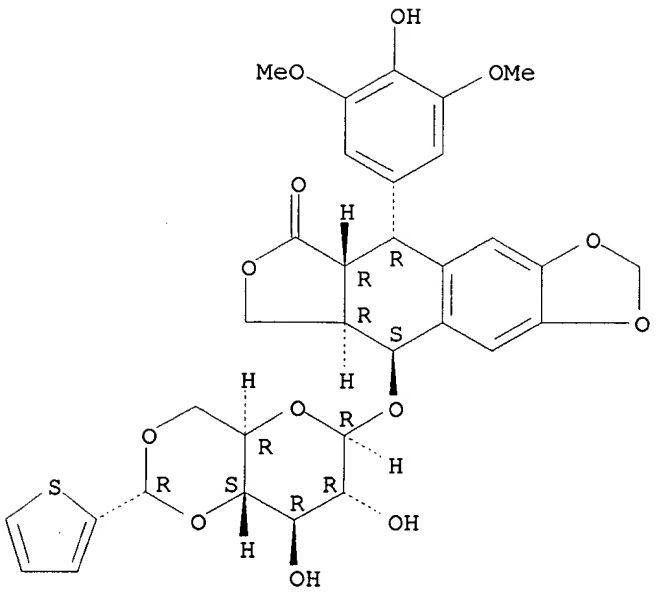


4182 REFERENCES IN FILE CA (1967 TO DATE)
85 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
4185 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 29767-20-2 REGISTRY
CN Furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-one,
5,8,8a,9-tetrahydro-5-

(4-hydroxy-3,5-dimethoxyphenyl)-9-[[4,6-O-[(R)-2-thienylmethylene]-.beta.-
D-glucopyranosyl]oxy]-, (5R,5aR,8aR,9S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Epipodophyllotoxin, 4'-demethyl-, 9-(4,6-O-2-thenylidene-.beta.-D-
glucopyranoside) (8CI)
CN Furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-one,
5,8,8a,9-tetrahydro-5-
(4-hydroxy-3,5-dimethoxyphenyl)-9-[[4,6-O-(2-thienylmethylene)-.beta.-D-
glucopyranosyl]oxy]-, [5R-[5.alpha.,5a.beta.,8a.alpha.,9.beta.(R*)]]-
CN Pyrano[3,2-d]-1,3-dioxin,
furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-
one deriv.
OTHER NAMES:
CN EPT
CN NSC 122819
CN **Teniposide**
CN teniposide VM-26
CN Vehem
CN VM 26
CN Vumon
FS STEREOSEARCH
DR 23362-13-2, 31514-29-1, 35317-44-3
MF C32 H32 O13 S
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, BEILSTEIN*, BIOBUSINESS,
BIOSIS,
BIOTECHNO, CA, CANCERLIT, CAPLUS, CBNB, CHEMCATS, CHEMLIST, CIN, CSNB,
DDFU, DIOGENES, DRUGNL, DRUGU, DRUGUPDATES, EMBASE, HSDB*, IPA,
MEDLINE,
MRCK*, NAPRALERT, NIOSHTIC, PHAR, PROMT, RTECS*, TOXLINE, TOXLIT,
ULIDAT, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry. Rotation (-).



784 REFERENCES IN FILE CA (1967 TO DATE)
21 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
785 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L19 ANSWER 1 OF 2 USPATFULL
AB The present invention provides solid pharmaceutical compositions for improved delivery of a wide variety of pharmaceutical active ingredients contained therein or separately administered. In one embodiment, the solid pharmaceutical **composition** includes a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate. The encapsulation coat can include different combinations of pharmaceutical active ingredients, hydrophilic surfactant, lipophilic surfactants and triglycerides. In another embodiment, the solid pharmaceutical **composition** includes a solid carrier, the solid carrier being formed of different combinations of pharmaceutical active ingredients, hydrophilic surfactants, lipophilic surfactants and triglycerides. The compositions of the present invention can be used for improved delivery of hydrophilic or hydrophobic pharmaceutical active ingredients, such as drugs, nutrionals, cosmeceuticals and diagnostic agents.
AN 2001:93131 USPATFULL
TI Solid carriers for improved delivery of active ingredients in pharmaceutical compositions
IN Patel, Mahesh V., Salt Lake City, UT, United States
Chen, Feng-Jing, Salt Lake City, UT, United States
PA Lipocine, Inc., Salt Lake City, UT, United States (U.S. corporation)
PI US 6248363 B1 20010619
AI US 1999-447690 19991123 (9)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Spear, James M.
LREP Reed, Dianne E.Reed & Associates
CLMN Number of Claims: 57
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 3302
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Solid carriers for improved delivery of active ingredients in pharmaceutical compositions
AB . . . delivery of a wide variety of pharmaceutical active ingredients contained therein or separately administered. In one embodiment, the solid pharmaceutical **composition** includes a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate. The encapsulation coat. . . can include different combinations of pharmaceutical active ingredients, hydrophilic surfactant, lipophilic surfactants and triglycerides. In another embodiment, the solid pharmaceutical **composition** includes a solid carrier, the solid carrier being formed of different combinations of pharmaceutical active ingredients, hydrophilic surfactants, lipophilic surfactants. . .
SUMM Hydrophobic active ingredients, such as progesterone, cyclosporine, itraconazole and glyburide present delivery challenges due to their poor **aqueous** solubility and slow dissolution rate. Several commercial products of these hydrophobic drugs are available, the various products using different methods. . . processing and stability challenges, as well as dissolution limitations, since the micronized/nanosized drug still possesses a high degree of crystallinity. **Liquid** formulations present drug precipitation and packaging challenges, due to

solvent evaporation. Moreover, non-solid formulations are more prone to chemical instability. . .

SUMM For hydrophilic active ingredients, the formulation challenges are different. Although these compounds are readily soluble in the **aqueous** gastrointestinal environment, they are poorly absorbed, due to poor membrane permeability and/or enzymatic degradation. Surfactants and lipophilic additives have been. . .

SUMM . . . stomach, thus making the performance less prone to gastric emptying variability. Further, the problems of leakage and other disadvantages of **liquid** formulations are not present in solid carrier formulations. To date, however, such solid carrier formulations generally have been limited to. . .

SUMM In one embodiment, the solid pharmaceutical **composition** includes a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate. The encapsulation coat. . .

SUMM In another embodiment, the solid pharmaceutical **composition** includes a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate. The encapsulation coat. . .

SUMM In another embodiment, the solid pharmaceutical **composition** includes a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate. The encapsulation coat. . .

SUMM In another embodiment, the solid pharmaceutical **composition** includes a solid carrier, wherein the solid carrier is formed of at least two components selected from the group consisting. . .

DRWD FIG. 1 is a graph showing the extent of dissolution/release of glyburide as a function of time for a **composition** according to the present invention and two prior art compositions.

DRWD . . . dissolution/release of omeprazole as a function of time for two compositions according to the present invention and a prior art **composition**.

DETD . . . delivery of a wide variety of pharmaceutical active ingredients contained therein or separately administered. In one embodiment, the solid pharmaceutical **composition** includes a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate. The encapsulation coat. . . can include different combinations of pharmaceutical active ingredients, hydrophilic surfactant, lipophilic surfactants and triglycerides. In another embodiment, the solid pharmaceutical **composition** includes a solid carrier, the solid carrier being formed of different combinations of pharmaceutical active ingredients, hydrophilic surfactant, lipophilic surfactants. . .

DETD . . . of the compositions of the present invention can be used as supplied commercially, or can be preprocessed by agglomeration, air **suspension** chilling, air **suspension** drying, balling, coacervation. comminution, compression, pelletization, cryopelletization, extrusion, granulation, homogenization, inclusion complexation, lyophilization, melting, mixing, molding, pan coating, solvent dehydration,. . .

DETD . . . partially solubilized and dispersed, in the encapsulation coat.

Alternatively, the active ingredient can be provided separately from the solid pharmaceutical **composition**, such as for co-administration. Such active ingredients can be any compound or mixture of compounds having therapeutic or other value. . .

DETD . . . dantrolene, dexchlopheniramine, diclofenac, dicoumarol, digoxin, dihydro epiandrosterone, dihydroergotamine, dihydrotachysterol, dirithromycin, donepezil, efavirenz, eposartan, ergocalciferol,

ergotamine, essential fatty acid sources, etodolac, **etoposide**, famotidine, fenofibrate, fentanyl, fexofenadine, finasteride, flucanazole, flurbiprofen, fluvastatin, fosphenytion, frovatriptan, furazolidone, gabapentin, gemfibrozil, glibenclamide, glipizide, glyburide, glymepride, griseofulvin, halofantrine, ibuprofen,. . . rimexolone, ritanovir, rizatriptan, rosigiltazone, saquinavir, sertraline, sibutramine, sildenafil citrate, simvastatin, sirolimus, spironolactone, sumatriptan, tacrine, tacrolimus, tamoxifen, tamsulosin,
targretin, tazarotene, telmisartan, **teniposide**, terbinafine, terzosin, tetrahydrocannabinol, tiagabine, ticlidopine, tirofibran, tizanidine, topiramate, topotecan, toremifene, tramadol, tretinoin, troglitazone, trovafloxacin, ubidecarenone, valsartan, venlafaxine, vertoporfin, vigabatrin, vitamin. . .

DETD . . . cyclosporine, danazol, dantrolene, dexchlopheniramine, diclofenac, digoxin, dihydro epiandrosterone, dihydroergotamine, dihyrotachysterol, dirithromycin, donepezil, efavirenz, ergocalciferol, ergotamine, essential fatty acid sources, etodolac, **etoposide**, famotidine, fenofibrate, fentanyl, fexofenadine, finasteride, flucanazole, flurbiprofen, fluvastatin, fosphenytion, frovatriptan, furzolidone, gabapentin, gemfibrozil, glibenclamide, glipizide, glyburide. glymepride, griseofulvin, halofantrine, ibuprofen,. . . rifabutine, rifapentine, rimexolone, ritanovir, rizatriptan, rosigiltazone, saquinavir, sibutramine, sildenafil citrate, simvastatin,
sirolimus, spironolactone, sumatriptan, tacrine, tacrolimus, tamoxifen, tamsulosin, targretin, tazarotene, **teniposide**, terbinafine, tetrahydrocannabinol, tiagabine, tizanidine, topiramate, topotecan, toremifene, tramadol, tretinoin, troglitazone, trovafloxacin, vertoporfin, vigabatrin, vitamin A, vitamin D, vitamin E, vitamin. . .

DETD . . . clemastine, coenzyme Q10, cyclosporine, danazol, dantrolene, dexchlopheniramine, diclofenac, dihydro epiandrosterone, dihydroergotamine, dihyrotachysterol, efavirenz, ergocalciferol, ergotamine, essential fatty acid sources, etodolac, **etoposide**, famotidine, fenofibrate, fexofenadine, finasteride, flucanazole, flurbiprofen, fosphenytion, frovatriptan, furzolidone, glibenclamide, glipizide, glyburide, glymepride, ibuprofen, irinotecan, isotreinoin, itraconazole, ivermectin, ketoconazole, ketorolac,. . . rabeprazole, raloxifene, refocoxib, repaglinide, rifabutine, rifapentine, rimexolone,
ritanovir, rizatriptan, rosigiltazone, saquinavir, sildenafil citrate, simvastatin, sirolimus, tacrolimus, tamoxifen, tamsulosin, targretin, tazarotene, **teniposide**, terbenafine, tetrahydrocannabinol, tiagabine, tizanidine, topiramate, topotecan, toremifene, tramadol, tretinoin, troglitazone, trovafloxacin, ubidecarenone, vigabatrin, vitamin A, vitamin D, vitamin E, vitamin. . .

DETD . . . and have greater solubility in oils, whereas surfactants with higher HLB values are more hydrophilic, and have greater solubility in **aqueous** solutions.

DETD **Polyglycerol** esters of fatty acids are also suitable surfactants for the present invention. Examples of suitable polyglyceryl
esters are shown in. . .

DETD 2.15. **Polyoxyethylene**-Polyoxypropylene Block Copolymers

DETD where "a" and "b" denote the number of **polyoxyethylene** and polyoxypropylene units, respectively.

DETD . . . N-methyl taurocholate
Sodium lithocholate
PHOSPHOLIPIDS
Egg/Soy lecithin [Epikuron .TM. (Lucas Meyer),
Ovothin .TM. (Lucas Meyer)]
Lyso egg/soy lecithin
Hydroxylated lecithin
Lysophosphatidylcholine
Cardiolipin

Sphingomyelin
Phosphatidyichoiine
Phosphatidyl effianolamine
Phosphatidic acid
Phosphatidyl glycerol
Phosphatidyl serine
PHOSPHORIC ACID ESTERS
Diethanolammonium **polyoxyethylene**-10 oleyl ether phosphate
Esterification products of fatty alcohols or fatty alcohol ethoxylates with phosphoric acid or anhydride
CARBOXYLATES
Ether carboxylates (by oxidation of terminal
OH. . . carnitine
Hexadecyl triammonium bromide
Decyl trimethyl ammonium bromide
Cetyl trimethyl ammonium bromide
Dodecyl ammonium chloride
Alkyl benzyldimethylammonium salts
Diisobutyl phenoxyethoxydimethyl benzylammonium salts
Alkylpyridinium salts
Betaines (trialkylglycine):
Lauryl betaine (N-lauryl,N,N-dimethylglycine)
Ethoxylated amines:
Polyoxyethylene-15 coconut amine

DETD . . . also useful surfactants for the compositions of the present invention. An example of such a derivative is tocopheryl PEG-1000 succinate (**TPGS**, available from Eastman).

DETD Preferred non-ionic hydrophilic surfactants include alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; **polyoxyethylene** alkyl ethers; **polyoxyethylene** alkylphenols; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; **polyoxyethylene** sorbitan fatty acid esters; **polyoxyethylene**-polyoxypropylene block copolymers; **polyglycerol** fatty acid esters; **polyoxyethylene** glycerides; **polyoxyethylene** sterols, derivatives, and analogues thereof; **polyoxyethylene** vegetable oils; **polyoxyethylene** hydrogenated vegetable oils; reaction mixtures of polyols with fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sugar esters,. . .

DETD More preferably, the non-ionic hydrophilic surfactant is selected from the group consisting of **polyoxyethylene** alkylethers; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; **polyoxyethylene** sorbitan fatty acid esters; **polyoxyethylene**-polyoxypropylene block copolymers; polyglyceryl fatty acid esters; **polyoxyethylene** glycerides; **polyoxyethylene** vegetable oils; and **polyoxyethylene** hydrogenated vegetable oils. The glyceride can be a monoglyceride, diglyceride, triglyceride, or a mixture.

DETD Preferred lipophilic surfactants are alcohols; **polyoxyethylene** alkylethers; fatty acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; **polyoxyethylene** glycerides; lactic acid derivatives of mono/diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; **polyoxyethylene** sorbitan fatty acid esters; **polyoxyethylene**-polyoxypropylene block copolymers; transesterified vegetable oils; sterols; sterol derivatives; sugar esters; sugar ethers; sucroglycerides; **polyoxyethylene** vegetable oils; and **polyoxyethylene** hydrogenated vegetable oils.

DETD . . . consisting of fatty acids; lower alcohol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; **polyoxyethylene** glycerides; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lactic acid derivatives of mono/diglycerides; sorbitan fatty acid esters;

polyoxyethylene sorbitan fatty acid esters; **polyoxyethylene**-polyoxypropylene block copolymers; **polyoxyethylene** vegetable oils; **polyoxyethylene** hydrogenated vegetable oils; and reaction mixtures of polyols and fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

DETD . . . acid esters; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lactic acid derivatives of mono/diglycerides; sorbitan fatty acid esters; **polyoxyethylene** vegetable oils; and mixtures thereof, with glycerol fatty acid esters and acetylated glycerol fatty acid esters being most preferred. Among. . .

DETD . . . a solid. For example, the encapsulation coat on the substrate may act as a solid "shell" surrounding and encapsulating a **liquid** or semi-**liquid** substrate material. Such substrates are also within the scope of the present invention, as it is ultimately the carrier, of. . .

DETD . . . encapsulation coat, or contained within the components forming the solid carrier. Alternatively, the additives can be contained in the pharmaceutical **composition** but not part of the solid carrier itself. Specific, non-limiting examples of additives are described below.

DETD . . . involving the preparation of the solid carrier, the encapsulation coating, or the pharmaceutical dosage form. These processes include agglomeration, air **suspension** chilling, air **suspension** drying, balling, coacervation, comminution, compression, pelletization, cryopelletization, extrusion, granulation, homogenization, inclusion complexation, lyophilization, nanoencapsulation. melting, mixing, molding, pan coating, solvent. . .

DETD . . . can optionally include one or more solubilizers, i.e., additives to increase the solubility of the pharmaceutical active ingredient or other **composition** components in the solid carrier. Suitable solubilizers for use in the compositions of the present invention include:

DETD . . . alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcutol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, **polyvinylalcohol**, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives;

DETD . . . of bioacceptable amounts, for example, to maximize the concentration of active ingredient, with excess solubilizer removed prior to providing the **composition** to a patient using conventional techniques, such as distillation or evaporation.

DETD . . . toxicity, specificity of the proteases and the potency of the inhibition. The inhibitor can be suspended or solubilized in the **composition** preconcentrate, or added to the **aqueous** diluent or as a beverage.

DETD coolants, such as halogenated hydrocarbons (e.g., trichloroethane, trichloroethylene, dichloromethane, fluorotrichloromethane), diethylether and **liquid** nitrogen;

DETD The compositions of the present invention can be processed by agglomeration, air **suspension** chilling, air **suspension** drying, balling, coacervation, coating, comminution, compression, cryopelletization, encapsulation, extrusion, wet granulation, dry granulation, homogenization, inclusion complexation, lyophilization, melting, microencapsulation, mixing,. . . the form of a minicapsule, a capsule, a tablet, an implant, a troche, a lozenge (minitablet), a temporary or permanent **suspension**, an ovule, a suppository, a wafer, a chewable tablet, a quick or fast dissolving tablet, an effervescent tablet, a buccal. . .

DETD The pharmaceutical **composition** and/or the solid carrier particles can be coated with one or more enteric coatings, seal coatings, film coatings, barrier coatings,. . . to those skilled in the art. In addition, the dosage form release profile can be effected by

a polymeric matrix **composition**, a coated matrix **composition**, a multiparticulate **composition**, a coated multiparticulate **composition**, an ion-exchange resin-based **composition**, an osmosis-based **composition**, or a biodegradable polymeric **composition**. Without wishing to be bound by theory, it is believed that the release may be effected through favorable diffusion, dissolution,. . .

DETD . . . mixture of pharmaceutically acceptable excipients which is applied to, combined with, mixed with or otherwise added to the carrier or **composition**. The coating may be applied to a compressed or molded or extruded tablet, a gelatin capsule, and/or pellets, beads, granules or particles of the carrier or **composition**. The coating may be applied through an **aqueous** dispersion or after dissolving in appropriate solvent. Additional additives and their levels, and selection of a primary coating material or. . .

DETD . . . also be formulated as enteric coated delayed release oral dosage forms, i.e., as an oral dosage form of a pharmaceutical **composition** as described herein which utilizes an enteric coating to effect release in the lower gastrointestinal tract. The enteric coated dosage. . . or molded or extruded tablet/mold (coated or uncoated) containing granules, pellets, beads or particles of the active ingredient and/or other **composition** components, which are themselves coated or uncoated. The enteric coated oral dosage form may also be a capsule (coated or uncoated) containing pellets, beads or granules of the solid carrier or the **composition**, which are themselves coated or uncoated.

DETD . . . copolymers. The Eudragit series E, L, S, RL, RS and NE (Rohm Pharma) are available as solubilized in organic solvent, **aqueous** dispersion, or dry powders. The Eudragit series RL, NE, and RS are insoluble in the gastrointestinal tract but are permeable. . .

DETD . . . vary based on the degree and type of substitution. Cellulose acetate phthalate (CAP) dissolves in pH>6. Aquateric (FMC) is an **aqueous** based system and is a spray dried CAP psuedolatex with particles <1 .mu.m. Other components in Aquateric can include pluronics,. . .

DETD . . . 5.5, and AS-HG (HF), which dissolves at higher pH. These polymers are offered as granules, or as fine powders for **aqueous** dispersions;

DETD . . . known to be insoluble in gastrointestinal fluids having pH below 5.5, generally 1.5-5.5, i.e., the pH generally present in the **fluid** of the upper gastrointestinal tract, but readily soluble or partially soluble at pH above 5.5, i.e., the pH generally present in the **fluid** of lower gastrointestinal tract.

DETD Another methacrylic acid polymer which is suitable for use in coating the **composition** or solid carrier which can be employed in the compositions and methods described herein, either alone or in combination with. . . used in combination with Eudragit L-30-D.RTM, soluble in intestinal fluids above pH 5.5, in order to effect a delayed release **composition**. The more Eudragit L-30 D.RTM used the more proximal release and delivery begins, and the more Eudragit S.RTM used, the. . .

DETD . . . cationic methacrylate copolymer with a water soluble cellulose ether. In powder form, it is readily dispensible into an easily sprayable **suspension** that dries to leave a smooth film. Such films rapidly disintegrate in **aqueous** media at a rate that is independent of pH and film thickness.

DETD . . . etc. It is also clear to one skilled in the art that appropriate additives can also be introduced to the **composition** or during the processes to facilitate the preparation of the solid carrier or the dosage forms, depending on the need. . .

DETD A coating process frequently involves spraying a coating **solution** onto a substrate. The coating **solution** can be a molten **solution** of the encapsulation coat **composition** free of a dispersing medium. The coating **solution** can also be prepared by solubilizing or suspending the

composition of the encapsulation coat in an **aqueous** medium, an organic solvent, a supercritical **fluid**, or a mixture thereof. At the end of the coating process, the residual dispersing medium can be further removed to. . .

DETD A pelletization process typically involves preparing a molten **solution** of the **composition** of the solid carrier or a dispersion of the **composition** of the solid carrier solubilized or suspended in an **aqueous** medium, an organic solvent, a supercritical **fluid**, or a mixture thereof. Such **solution** or dispersion is then passed through a certain opening to achieve the desired shape, size, and other properties. Similarly, appropriate. . .

DETD . . . divided particles continuously, by a rolling or tumbling action on a flat or curved surface with the addition of a **liquid**.

DETD . . . A standard fluidized drier bowl can be replaced with a rotating plate as an air distributor. For granulation, a binder **liquid** is sprayed from via one or two binary nozzles located axially to the rotational movement of the powder bed. This. . . the granules to approximately spherical pellets. Such balling or agitation techniques can be influenced by operating conditions, such as bridging/binding **liquid** requirements, residence time of the material in the pelletizer, speed and angle of inclination of the pelletizer, amount of material. . .

DETD The components of the invention can also be self binding. **Liquid** components can be pelletized with an the aid of suitable solidifying, binding or thickening agents.

DETD Extrusion is a well-known method of applying pressure to a damp or melted **composition** until it flows through an orifice or a defined opening. The extrudable length varies with the physical characteristics of the. . .

DETD Encapsulation by Extrusion: In this method, the lipid **composition** in the form of an emulsion is added to a low moisture melt of low maltodextrin, or sugar, or modified edible starch, mixed and extruded into a cold bath. The solidified **composition** can be further ground down. Optionally, centrifugal extrusion can be utilized for efficiency.

DETD . . . into uniform lengths instantaneously and gradually transformed into spherical shapes. In addition, powdered raw materials, which require addition of either **liquid** or material from a mixer, can be processed in an air-assisted spheronizer.

DETD . . . properties of the additives used. The rate of feeding and inlet/outlet temperatures are adjusted to ensure congealing of the atomized **liquid** droplet. The feed should have adequate viscosity to ensure homogeneity. The conversion of molten feed into powder is a single,. . .

DETD . . . is particularly suitable for heat labile substances, since ambient temperature is used to dry, and for moisture sensitive substances, since non-**aqueous** compositions can be utilized. Spray congealing is similar to spray drying, except that no solvent is utilized. Spray congealing is. . .

DETD . . . pellets. The spray congealed particles may be used in tablet granulation form, encapsulation form, or can be incorporated into a **liquid suspension** form.

DETD . . . ingredients or additives to form an oil in water emulsion which is spray dried. This results in a homogenous solid **composition** . Furthermore, water or organic solvent based formulations can be spray dried by using inert process gas, such as nitrogen, argon. . .

DETD Nanoencapsulation involves solubilizing an **aqueous** **solution** of an active ingredient and other components in a weakly polar vehicle. **Micelles** are formed with the active in an organic outer phase. Then, an amphiphilic monomer is added to the lipophilic external phase. The mixed **micelles** thus formed are then polymerized with the aid of a suitable procedure, such as UV or

gamma radiation, heat, or chemical agents. The hardened solidified **micelles** are made to undergo phase exchange by replacing an outer lipophilic vehicle by water. By selecting appropriate monomers, networking agents. . .

DETD Supercritical **Fluid** Processes

DETD Components of the present invention can be dispersed in a supercritical **fluid** and crystallized as needed. Current techniques involving supercritical fluids include precipitation by rapid expansion of supercritical solutions, gas anti-solvent processes,. . .

DETD . . . coacervation phase into a phase in which there is a film around each particle. The coacervation method involves dispersing the **composition** in a dispersion of a polymeric colloid, such as gelatin alginate, and shock treating the mixture will temperature or pH,. . .

DETD The cryopelletization procedure allows conversion of a molten mass, **aqueous solution** or **suspension** into solid, bead-like particles. The molten mass solutions or suspensions are dripped by means of an appropriately designed device into **liquid** nitrogen. The production of small drops and **liquid** nitrogen cooling permit very rapid and uniform freezing of the material processed. The pellets are further dried in conventional freeze. . .

DETD Solvent Based **Solution** Coating

DETD Solvent-based coating is when the components of the invention are solubilized and/or dispersed in a solvent. The solvent can be **aqueous**. When the solvent is **aqueous**-based, the components can be emulsified with an appropriate emulsifier, organic solvent, or a supercritical **fluid**. Solvents with a lower melting point than water and higher evaporation numbers are preferred. Solvent mixtures with other organic solvents. . .

DETD Air **suspension** in a rotary fluidized bed granulator can used to deposit the encapsulation coat on to a substrate, thus allowing a high rate of drug application with low drug loss. Furthermore, both **aqueous** and organic solvents can be used. The Wurster process, an air **suspension** technique, is more suitable for encapsulations involving very fine powders.

DETD . . . molten state. The selection of proper coating materials depends on melting point, melting point range and the viscosity in the **liquid** state. A fluidized bed is ideal for molten coatings of substrates that range from about 100 microns to about 2000. . . particles that are suspended and separated from each other by the fluidization air enter a zone of finely atomized coating **liquid** . Coating occurs as the **liquid** droplets, which are substantially smaller in size than substrate, impact the particles, spread, and solidify. Multiple layers can be coated,. . . of spraying is followed by a product stabilization or cooling step. Some critical success parameters include bed temperature, atomization, atomization **fluid** temperature, or droplet size, spray type, spray rate, rate of coating droplet solidification on particle surfaces, particle size, shape, etc.. . .

DETD . . . additive aggregate starch or sugar bead. Instead, the compositions are processed, and the components are chosen, such that a solid **composition** is formed without the need to coat the **composition** onto a substrate bead. Such compositions can be in the form of beadlets, beads, granules, pellets, etc., that have an. . . distribution of active ingredient, surfactant, triglyceride and/or additives. These compositions can be produced by means of balling in pelletizers or **fluid** bed granulators, and compaction or extrusion/spheronization. In addition, these compositions can be produced using solvent-free spray congealing processes or dropping (globulization) methods. Dropping procedures involve conversion of **aqueous** solutions or suspensions to a solid form. Congealing of the **liquid** droplets in cooling baths can aided by a chemical

reaction (e.g., insoluble salt or complex formation), a sol/gel transition, or by freezing in a coolant bath of **liquid** nitrogen or halogenated hydrocarbons.

DETD In one embodiment, the solid pharmaceutical **composition** includes a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate. The encapsulation coat. . .

DETD A further advantage believed to accrue from the pharmaceutical compositions of the present invention is that upon administration of the **composition** to a patient, the high levels of surfactants and other components present in the **composition** facilitate the rapid solubilization of the pharmaceutical active ingredient. Thus, while the prior art **composition** of Harrison contains a drug in a form which requires further solubilization in vivo, such as by emulsification and micellization. . . in the gastrointestinal tract, the active ingredient in compositions of the present invention is at least partially solubilized in the **composition** itself, and is further provided with surfactants and other components in the **composition** to facilitate rapid dispersion (emulsification/micellization) and sustained solubilization of the active ingredient upon administration.

DETD . . . coat can alternatively be formulated without an active ingredient. In this aspect, an active ingredient can be provided in the **composition** itself but not in the encapsulation coat, if desired. While not presently preferred, such a formulation delivers the active ingredient. . .

DETD In another embodiment, the solid pharmaceutical **composition** includes a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate. The encapsulation coat. . . be present in amounts to enable at least partial solubilization of an active ingredient in the encapsulation coat, in the **composition**, or separately administered.

DETD In another embodiment, the solid pharmaceutical **composition** effectively presents a lipophilic component with or without an active ingredient to help promote absorption of a hydrophilic active.

DETD In another embodiment, the solid pharmaceutical **composition** includes a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate. The encapsulation coat. . .

DETD In another embodiment, the solid pharmaceutical **composition** includes a solid carrier, wherein the solid carrier is formed of at least two components selected from the group consisting. . .

DETD In this embodiment, the solid pharmaceutical **composition** is formulated without the need for a substrate seed particle. The active ingredient, surfactants and triglycerides in the chosen combination. . .

DETD The present invention also provides methods of using the above-described pharmaceutical **composition**. In one aspect, the present invention provides a method of treating a patient with a pharmaceutical active ingredient, the method including the steps of providing a dosage form of a pharmaceutical **composition** as described above, including an active ingredient, and administering the dosage form to the patient. The patient can be an. . .

DETD In another aspect, the present invention provides a method including the steps of providing a dosage form of a pharmaceutical **composition** as described above, providing a dosage form of a pharmaceutical active ingredient, and administering the dosage forms to the patient.. . . administered to the patient in a separate dosage form prior to, concurrently with, or subsequent to administration of the pharmaceutical **composition**.

DETD . . . improving the palatability and/or masking the taste of a pharmaceutical active ingredient, by providing the active ingredient in a pharmaceutical **composition** as described above. Since the active ingredient is encapsulated in a lipid coat, it will not instantaneously dissolve in the. . .

DETD . . . a method of improving the dissolution and/or absorption of a pharmaceutical active ingredient, by administering the active ingredient in a **composition** as described above, or co-administering the active ingredient with a **composition** as described above.

DETD A spraying **solution** of the coating materials was prepared by dissolving the desired amount of the active ingredient and mixing with the hydrophilic. . . and/or lipophilic surfactants in an organic solvent or a mixture of organic solvents. The organic solvent used for the coating **solution** was a mixture of methylene chloride and isopropyl alcohol in a 3:1 to 1:1 weight ratio.

DETD **Composition** I

DETD A pharmaceutical **composition** was prepared according to the method of Example 1, having a substrate particle, an active ingredient (glyburide), and a mixture. . .

DETD **Composition** II

DETD A pharmaceutical **composition** was prepared according to the method of Example 1, having a substrate particle, an active ingredient (progesterone), a mixture of. . .

DETD **Composition** III

DETD A pharmaceutical **composition** was prepared according to the method of Example 1, having a substrate particle, an active ingredient (itraconazole) a mixture of. . .

DETD **Composition** IV

DETD A pharmaceutical **composition** was prepared according to the method of Example 1, having a substrate particle, an active ingredient (omeprazole), a mixture of. . .

DETD . . . seal coated by a polymer layer. The seal coating polymer layer was applied to the progesterone-coated beads in a Uni-Glatt **fluid** bed coater. Polyvinylpyrrolidone (PVP-K30) was dissolved in isopropyl alcohol to form a 5% w/w **solution**. This seal coating **solution** was sprayed onto the coated beads with a Wurster bottom spray insert. The inlet and outlet air temperature were maintained. . .

DETD . . . protective polymer layer. The protective coating was applied to the omeprazole coated beads by spraying with a hydroxypropyl methylcellulose (HPMC) **solution**. The protective coating HPMC **solution** was prepared by dissolving 6 grams of HPMC in ethanol. To this **solution**, methylen chloride was added followed by 2 mL of triethylcitrate as a plasticizer and 1 g of talc. The HPMC **solution** was sprayed on the beads as described in Example 6, and the protective coated beads were then dried and collected.

DETD . . . with an enteric coating layer. The enteric layer was applied to the omeprazole coated beads by spraying a Eudragit L100 **solution**. Eudragit L100 is an acrylate polymer commercially available from Rohm Pharma. The spraying **solution** was prepared by dispersing 15 g of Eudragit L100 in 200 mL of ethanol to give a clear **solution**. To this **solution**, 4 g of triethyl citrate was then added as a plasticizer. 2 grams of purified talc was also added to the **solution**. The **solution** was then sprayed onto the beads, and the beads were dried, as described in Example 6.

DETD . . . time point, 3 mL of the medium was sampled, and the medium was replenished with 3 mL of fresh buffer/Tween **solution**. The samples were filtered through a 0.45.mu. filter immediately after the sampling. The filtrates were then diluted in methanol to. . .

DETD . . . time point, 3 mL of the medium was sampled, and the medium was replenished with 3 mL of fresh buffer/Tween **solution**. The samples were filtered through a 0.45.mu. filter immediately after the sampling. The filtrates were then diluted in methanol to. . .

DETD . . . appropriate amounts of the active ingredients in any given dosage form then can be administered together or separately with the **composition**. It should also be appreciated that the compositions can further include additional additives, excipients, and other components for the purpose of facilitating the processes involving the preparation of the **composition** or the pharmaceutical dosage form, as described herein, as is well-known to those skilled in the art.

CLM What is claimed is:

1. A pharmaceutical **composition** in the form of a solid carrier comprising a substrate and an encapsulation coat on the substrate, wherein the encapsulation. . .

2. The pharmaceutical **composition** of claim 1, wherein the active ingredient is a drug, a nutrient, a cosmeceutical, a diagnostic agent, a salt thereof,. . .

3. The pharmaceutical **composition** of claim 1, wherein the weight ratio of lipophilic additive to the at least one hydrophilic surfactant is in the. . .

4. The pharmaceutical **composition** of claim 1, wherein the active ingredient represents approximately 1.96 wt. % to 28.57 wt. % of the encapsulation coat.

. . .

5. The pharmaceutical **composition** of claim 3, wherein the active ingredient represents approximately 1.96 wt. % to 28.57 wt. % of the encapsulation coat.

. . .

6. A pharmaceutical **composition** in the form of a solid carrier comprising an admixture of a hydrophilic pharmaceutical active ingredient, an effective solubilizing amount. . .

7. The pharmaceutical **composition** of claim 6, wherein the weight ration of lipophilic additive to the at least one hydrophilic surfactant is in the. . .

8. The pharmaceutical **composition** of claim 6, wherein the active ingredient represents approximately 4.6 wt. % to 50.0 wt. % of the solid carrier.

. . .

9. The pharmaceutical **composition** of claim 1, wherein the hydrophilic active ingredient has an apparent water solubility of at least about 1 mg/mL.

10. The pharmaceutical **composition** of claim 9, wherein the active ingredient is a hydrophilic drug, a cytokine, a peptidomimetic, a

peptide, a protein, a. . .

11. The pharmaceutical **composition** of claim 9, wherein the active ingredient is selected from the group consisting of analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents,. . .

12. The pharmaceutical **composition** of claim 9, wherein the active ingredient is selected from the group consisting of acarbose; acyclovir; acetyl cysteine; acetylcholine chloride;. . .

13. The pharmaceutical **composition** of claim 9, wherein the active ingredient is selected from the group consisting of acarbose; acyclovir; atracurium besylate; alendronate; alglucerase;. . .

14. The pharmaceutical **composition** of claim 9, wherein the active ingredient is selected from the group consisting of acarbose; alendronate; amantadine hydrochloride; azithromycin; calcitonin. . .

15. The pharmaceutical **composition** of claim 1, wherein the at least one hydrophilic surfactant comprises a non-ionic hydrophilic surfactant having an HLB value of. . .

16. The pharmaceutical **composition** of claim 15, wherein the non-ionic hydrophilic surfactant is selected from the group consisting of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; **polyoxyethylene** alkyl ethers; **polyoxyethylene** alkylphenols; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters;

polyoxyethylene sorbitan fatty acid esters; **polyoxyethylene**-polyoxypropylene block copolymers; **polyglycerol** fatty acid esters; **polyoxyethylene** glycerides; **polyoxyethylene** sterols, derivatives, and analogues thereof; **polyoxyethylene** vegetable oils; **polyoxyethylene** hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides,. . .

17. The pharmaceutical **composition** of claim 1, wherein the at least one hydrophilic surfactant comprises an ionic surfactant.

18. The pharmaceutical **composition** of claim 17, wherein the ionic surfactant is selected from the group consisting of alkyl ammonium salts; bile acids and. . .

19. The pharmaceutical **composition** of claim 1, wherein the substrate is a powder or a multiparticulate.

20. The pharmaceutical **composition** of claim 1, wherein the substrate is an additive, an active ingredient or a mixture thereof.

21. The pharmaceutical **composition** of claim 20, wherein the substrate is an additive selected from the group consisting of a solubilizer, an enzyme inhibitor,. . .

22. The pharmaceutical **composition** of claim 19, wherein the substrate is a multiparticulate selected from the group consisting of a granule, a pellet, a. . .

23. The pharmaceutical **composition** of claim 1, wherein the solid carrier is a bead, a beadlet, a granule, a spherule, a pellet, a microcapsule,. . .

24. The pharmaceutical **composition** of claim 1, wherein the lipophilic additive is selected from the group consisting of lipophilic surfactants.

25. The pharmaceutical **composition** of claim 24, wherein the lipophilic additive is selected from the group consisting of alcohols; **polyoxyethylene** alkylethers; fatty acids; bile acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; **polyoxyethylene** glycerides; lactic acid derivatives of mono/diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; **polyoxyethylene** sorbitan fatty acid esters; **polyoxyethylene**-polyoxypropylene block copolymers; transesterified vegetable oils; sterols; sterol derivatives; sugar esters; sugar ethers; sucroglycerides; **polyoxyethylene** vegetable oils; **polyoxyethylene** hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides,. . .

26. The pharmaceutical **composition** of claim 1, wherein the lipophilic additive is a triglyceride selected from the group consisiting of vegetable oils, fish oils,. . .

27. The pharmaceutical **composition** of claim 1, wherein the solid carrier is enteric coated, coated for fast disintegration, seal coated, film coated, barrier coated. . .

28. The pharmaceutical **composition** of claim 1, wherein the **composition** is encapsulated, extruded, compressed, pelletized, coated, mixed granulated, crystallized, lyophilized or molded.

29. The pharmaceutical **composition** of claim 1 in the form of a capsule, a table, an ovule, a suppository, a water, a chewable tablet. . . granule, a pellet, a bead, a pill, a sachet, a sprinkle, a film, a dry syrup, a reconstitutable solid, a **suspension**, a lozenge, a troche, an implant, a powder, a triturate, a platelet, or a strip.

30. The pharmaceutical **composition** of claim 1, wherein the **composition** is formulated for immediate release, pulsatile release, controlled release, extended release, delayed release, targeted release, or targeted delayed release.

31. The pharmaceutical **composition** of claim 1, wherein the **composition** is formulated for oral, nasal, ocular urethral, buccal, transmucosal, vaginal, topical or rectal delivery.

. . . administering an active ingredient to a mammal, the method comprising administering to the mammal a dosage from of the pharmaceutical **composition** of claim 1.

34. The pharmaceutical **composition** of claim 1, wherein the active ingredient is a drug, a nutrient, a cosmeceutical, a diagnostic agent, a salt thereof,. . .

35. The pharmaceutical **composition** of claim 6, wherein the hydrophilic active ingredient has an apparent water solubility of at least about 1 mg/mL.

36. The pharmaceutical **composition** of claim 35, wherein the active ingredient is a hydrophilic drug, a cytokine, a peptidomimetic, a peptide, a protein, a. . .

37. The pharmaceutical **composition** of claim 35, wherein the active ingredient is selected form the group consisting of analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents,. . .

38. The pharmaceutical **composition** of claim 35 wherein the active ingredient is selected from the group consisting of acarbose; acyclovir; acetyl cysteine; acetylcholine chloride;. . .

39. The pharmaceutical **composition** of claim 35, wherein the active ingredient is selected from the group consisting of acarbose; acyclovir; atracurium besylate; alendronate; alglucerase;. . .

40. The pharmaceutical **composition** of claim 35, wherein the active ingredient is selected from the group consisting of acarbose; alendronate; amantadine hydrochloride; azithromycin; calcitonin. . .

41. The pharmaceutical **composition** of claim 6, wherein the at least one hydrophilic surfactant comprises a non-ionic hydrophilic surfactant having an HLB value of. . .

42. The pharmaceutical **composition** of claim 41, wherein the non-ionic hydrophilic surfactant is selected from the group consisting of alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; **polyoxyethylene** alkyl ethers; **polyoxyethylene** alkylphenols; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; **polyoxyethylene** sorbitan fatty acid esters; **polyoxyethylene**-polyoxypropylene block copolymers; **polyglycerol** fatty acid esters; **polyoxyethylene** glycerides; **polyoxyethylene** sterols, derivatives, and analogues thereof; **polyoxyethylene** vegetable oils; **polyoxyethylene** hydrogenated vegetable oils; reactioli mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides,. . .

43. The pharmaceutical **composition** of claim 6, wherein the at least one hydrophilic surfactant comprises an ionic surfactant.

44. The pharmaceutical **composition** of claim 43, wherein the ionic surfactant is selected from the group consisting of alkyl ammonium salts; bile acids and. . .

45. The pharmaceutical **composition** of claim 6, wherein the solid carrier is a bead, a beadlet, a granule, a spherule, a pellet, a

microcapsule,. . .

46. The pharmaceutical **composition** of claim 6, which further comprises a solubilizer, an enzyme inhibitor, an anti-adherent, an anticoagulant, an antifoaming agent, an antioxidant,. . .

47. The pharmaceutical **composition** of claim 6, wherein the lipophilic additive is selected from the group consisting of lipophilic surfactants.

48. The pharmaceutical **composition** of claim 47, wherein the lipophilic additive is selected from the group consisting of alcohols; **polyoxyethylene** alkylethers; fatty acids; bile acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; **polyoxyethylene** glycerides; lactic acid derivatives of mono/diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; **polyoxyethylene** sorbitan fatty acid esters; **polyoxyethylene**-polyoxypropylene block copolymers; transerterified vegetable oils; sterols; sterol derivatives; sugar esters; sugar others; sucroglycerides; **polyoxyethylene** vegetable oils; **polyoxyethylene** hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides,. . .

49. The pharmaceutical **composition** of claim 6, wherein the lipophilic additive is a triglyceride selected from the group consisting of vegetable oils, fish oils,. . .

50. The pharmaceutical **composition** of claim 6, wherein the solid carrier is enteric coated, coated for fast disintegration, seal coated, film coated, barrier coated,. . .

51. The pharmaceutical **composition** of claim 6, wherein the **composition** is encapsulated, extruded, compressed, pelletized, coated, mixed, granulated, crystallized, lyophilized or molded.

52. The pharmaceutical **composition** of claim 6 in the form of a capsule, a tablet, an ovule, a suppository, a wafer, a chewable tablet,. . . granule, a pellet, a bead, a pill, a sachet, a sprinkle, a film, a dry syrup, a reconstitutable solid, a **suspension**, a lozenge, a troche, an implant, a powder, a triturate, a platelet, or a strip.

53. The pharmaceutical **composition** of claim 6, wherein the **composition** is formulated for immediate release, pulsatile release, controlled release, extended release, delayed release, targeted release, or targeted delayed release.

54. The pharmaceutical **composition** of claim 6, wherein the **composition** is formulated for oral, nasal, ocular, urethral, buccal, transmucosal, vaginal, topical or rectal delivery.

. . . administering an active ingredient to a mammal, the method comprising administering to the mammal a dosage form of the pharmaceutical **composition** of claim 6.

57. The pharmaceutical **composition** of claim 7, wherein the active ingredient represents approximately 4.6 wt. % to 50.0 wt. % of the solid carrier.

. . .

L19 ANSWER 2 OF 2 USPATFULL

AB Compositions and methods are provided for the modulation of expression of cellular adhesion molecules. In accordance with preferred

embodiments, oligonucleotides are provided which are specifically hybridizable with nucleic acids encoding intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and endothelial leukocyte adhesion molecule-1. Methods of modulating expression of cellular adhesion molecules are provided, as are methods of treating conditions associated with cellular adhesion molecules. In a preferred embodiment, the cellular adhesion molecule is ICAM-1, and a preferred antisense sequence targeted to human ICAM-1 is demonstrated to have clinical utility in several disease indications.

AN 2000:98407 USPATFULL

TI Antisense modulation of cell adhesion molecule expression and treatment of cell adhesion molecule-associated diseases

IN Bennett, C. Frank, Carlsbad, CA, United States
Mirabelli, Christopher K., Dover, MA, United States
Baker, Brenda, Carlsbad, CA, United States

PA Isis Pharmaceuticals Inc., Carlsbad, CA, United States (U.S. corporation)

PI US 6096722 20000801

AI US 1998-85759 19980527 (9)

RLI Continuation-in-part of Ser. No. US 1995-440740, filed on 12 May 1995, now patented, Pat. No. US 5843738 which is a continuation-in-part of Ser. No. US 1993-63167, filed on 17 May 1993, now patented, Pat. No. US 5514788 which is a continuation of Ser. No. US 1993-969151, filed on 10 Feb 1993, now abandoned which is a continuation-in-part of Ser. No. US 1993-7997, filed on 21 Jan 1993, now patented, Pat. No. US 5591623 which is a continuation-in-part of Ser. No. US 1992-939855, filed on 2 Sep 1992, now abandoned which is a continuation-in-part of Ser. No. US 1990-567286, filed on 14 Aug 1990, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Elliott, George C.; Assistant Examiner: Epps, Janet

LREP Law Offices of Jane Massey Licata

CLMN Number of Claims: 22

ECL Exemplary Claim: 1

DRWN 15 Drawing Figure(s); 25 Drawing Page(s)

LN.CNT 4765

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Antisense modulation of cell adhesion molecule expression and treatment of cell adhesion molecule-associated diseases

DRWD . . . this invention, to "contact" tissues or cells with an oligonucleotide or oligonucleotides means to add the oligonucleotide(s), usually in a **liquid** carrier, to a cell **suspension** or tissue sample, either in vitro or ex vivo, or to administer the oligonucleotide(s) to cells or tissues within an. . .

DRWD . . . treatment, oligonucleotides are administered in accordance with this invention. Oligonucleotide compounds of the invention may be formulated in a pharmaceutical **composition**, which may include pharmaceutically acceptable carriers, thickeners, diluents, buffers, preservatives, surface active agents, neutral or cationic lipids, lipid complexes, liposomes,. . .

DRWD Surfactants include, for example, sodium lauryl sulfate, **polyoxyethylene**-9-lauryl ether and **polyoxyethylene**-20-cetyl ether (Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems 1991, page 92); and perfluorochemical emulsions, such as FC-43. . .

DRWD . . . other pharmacologically inert vehicle for delivering one or more nucleic acids to an animal. The pharmaceutically acceptable carrier may be **liquid** or solid and is selected with the planned manner of administration in mind so as to provide for the desired bulk, consistency, etc., when combined with a nucleic acid and the other

components of a given pharmaceutical **composition**. Typical pharmaceutically acceptable carriers include, but are not limited to, binding agents (e.g., pregelatinized maize starch, polyvinyl-pyrrolidone or hydroxypropyl methylcellulose,. . .

DRWD . . . astringents, local anesthetics or anti-inflammatory agents, or may contain additional materials useful in physically formulating various dosage forms of the **composition** of present invention, such as dyes, flavoring agents, preservatives, antioxidants, opacifiers, thickening agents and stabilizers. However, such materials, when added,. . .

DRWD . . . Colloidal dispersion systems include, but are not limited to, macromolecule complexes, nanocapsules, microspheres, beads and lipid-based systems including oil-in-water emulsions, **micelles**, mixed **micelles**, liposomes and lipid:oligonucleotide complexes of uncharacterized structure. A preferred colloidal dispersion system is a plurality of liposomes. Liposomes are microscopic spheres having an **aqueous** core surrounded by one or more outer layers made up of lipids arranged in a bilayer configuration (see, generally, Chonn. . .

DRWD . . . when local delivery of a drug is desired at, or immediately adjacent to, the point of application of the drug **composition** or formulation. Three general types of topical routes of administration include administration of a drug **composition** to mucous membranes, skin or eyes. Compositions for topical administration may be a mixture of components or phases as are. . .

DRWD . . . topical administration may include transdermal patches, ointments, lotions, creams, emulsions, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, **aqueous**, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may. . . present invention may be formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, **liquid** syrups, soft gels, suppositories, and enemas.

DRWD The compositions of the present invention may also be formulated as suspensions in **aqueous**, non-**aqueous** or mixed media. **Aqueous** suspensions may further contain substances which increase the viscosity of the **suspension** including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The **suspension** may also contain stabilizers.

DRWD . . . the compositions of the present invention. Compositions for oral administration include powders or granules, suspensions or solutions in water or non-**aqueous** media, capsules, sachets or tablets. Enteric coatings may be useful. Thickeners, flavoring agents, diluents, emulsifiers, dispersing aids or binders may. . .

DRWD For pulmonary administration aerosolization of **liquid** particles may be preferred; this can be achieved by any suitable means, such as with a nebulizer. See, for example,. . . PRONEB Compressor with LC PLUS, PARI WALKHALER Compressor/Nebulizer System, PARI LC PLUS Reusable Nebulizer, and PARI LC Jet+ .RTM.Nebulizer. Preferably, **liquid** or solid aerosols are produced at a rate of from about 10 to 150 liters per minute, more preferably from. . . and most preferably about 60 liters per minute. Exemplary formulations for use in nebulizers consist of an oligonucleotide in a **liquid**, such as sterile, pyragen free water, or saline **solution**, wherein the oligonucleotide comprises up to about 40% w/w of the formulation. Preferably, the oligonucleotide comprises less than 20% w/w.. . . If desired, further additives such as preservatives (for example, methyl hydroxybenzoate) antioxidants, and flavoring agents can be added to the **composition**.

DRWD Compositions for parenteral administration may include sterile **aqueous** solutions which may also contain buffers, diluents and

other suitable additives.

DRWD . . . al., FASEB J., 1994, 8, 504). Administration of the antisense compounds of the invention, as part of an appropriate pharmaceutical **composition** if required, to an animal is expected to inhibit diapedesis and subsequent undesired immunoresponsive events such as, for example, inflammation. . .

DRWD . . . preparation if required, to the animal. Such administration can be systemic or directly to involved tissues such as, e.g., synovial **fluid**. Increased expression of cellular adhesion molecules, including ELAM-1, VCAM-1, ICAM-1 and PECAM-1, has been detected in synovial **fluid** from patients having rheumatoid arthritis (Tak et al., Clin. Immunol. Immunopathol., 1995, 77, 236). Such forms of arthritis include, for. . .

DRWD . . . Steinman, Sci. Amer., 1993, 269, 107). Administration of the antisense compounds of the invention, as part of an appropriate pharmaceutical **composition** if required, to an animal is expected to prevent or inhibit the development of the autoimmune disease and subsequent undesired. . .

DRWD . . . European Heart J., 1997, 18, 470). Administration of the antisense compounds of the invention, as part of an appropriate pharmaceutical **composition** if required, to an animal is expected to modulate MI/R injury. Such administration can be systemic or directly to the. . .

DRWD . . . et al., Stroke, 1997, 28, 2031). Administration of the antisense compounds of the invention, as part of an appropriate pharmaceutical **composition** if required, to an animal is expected to stroke-related injuries. Such administration can be systemic or directly to the circulatory. . .

DRWD . . . antisense compounds and one or more other chemotherapeutic agents, are to be administered simultaneously in a treatment regime, one preferred **composition** is one comprising a lipid vesicle, particularly a sterically stabilized lipid vesicle, comprising both (or all) of the compounds. In. . .

DRWD . . . can be administered simultaneously as described above. Combination treatments can also be carried out by first (1) administering a first **composition** comprising a first antisense compound targeted to a cellular adhesion molecule (or a combination thereof with one or more anti-inflammatory, immunosuppressive and/or chemotherapeutic agents) for a first period of time and then (2) "switching" to administration of a second **composition** comprising a second antisense compound targeted to a cellular adhesion molecule (or a combination thereof with one or more anti-inflammatory. . .

DRWD . . . melphalan, methylcyclohexylnitrosurea, cyclophosphamide, 6-mercaptopurine, 6-thioguanine, cytarabine (CA), 5-azacytidine, hydroxyurea, deoxycoformycin, colchicine, 5-fluorouracil (5-FU), 4-hydroxyperoxycyclophosphoramide, 5-fluorodeoxyuridine (5-FUdR), methotrexate (MTX), vincristine, vinblastine, **etoposide**, trimetrexate, **teniposide**, cisplatin and diethylstilbestrol (DES). (See, generally, The Merck Manual of Diagnosis and Therapy, 15th Ed., pp. 1206-1228, Berkow et al.,. . .

DETD . . . stirring, allowing the evolved carbon dioxide gas to be released in a controlled manner. After 1 hour, the slightly darkened **solution** was concentrated under reduced pressure. The resulting syrup was poured into diethylether (2.5 L), with stirring. The product formed a. . . gum. The ether was decanted and the residue was dissolved in a minimum amount of methanol (ca. 400 mL). The **solution** was poured into fresh ether (2.5 L) to yield a stiff gum. The ether was decanted and the gum was. . .

DETD . . . pre-heated oil bath at 160.degree. C. After heating for 48

hours at 155-160.degree. C., the vessel was opened and the **solution** evaporated to dryness and triturated with MeOH (200 mL). The 10 residue was suspended in hot acetone (1 L). The. . .

DETD A first **solution** was prepared by dissolving 3'-O-acetyl-2'-O-methoxyethyl-5'-O-dimethoxytrityl-5-methyluridine (96 g, 0.144 M) in CH.sub.3 CN (700 mL) and set aside. Triethylamine (189 mL, 1.44 M) was added to a **solution** of triazole (90 g, 1.3 M) hin CH.sub.3 CN (1 L), cooled to -5.degree. C. and stirred for 0.5 h using an overhead stirrer. POCl.sub.3 was added dropwise, over a 30 minute period, to the stirred **solution** maintained at 0-10.degree. C., and the resulting mixture stirred for an additional 2 hours. The first **solution** was added dropwise, over a 45 minute period, to the later **solution**. The resulting reaction mixture was stored overnight in a cold room. Salts were filtered from the reaction mixture and the **solution** was evaporated. The residue was dissolved in EtOAc (1 L) and the insoluble solids were removed by filtration. The filtrate. . .

DETD A **solution** of 3'-O-acetyl-2'-O-methoxyethyl-5'-O-dimethoxytrityl-5-methyl-4-triazoleuridine (103 g, 0.141 M) in dioxane (500 mL) and NH.sub.4 OH (30 mL) was stirred at room temperature for 2 hours. The dioxane **solution** was evaporated and the residue azeotroped with MeOH (2.times.200 mL). The residue was dissolved in MeOH (300 mL) and transferred. . .

DETD . . . to be 95% complete). The reaction mixture was extracted with saturated NaHCO.sub.3 (1.times.300 mL) and saturated NaCl (3.times.300 mL). The **aqueous** washes were back-extracted with CH.sub.2 Cl.sub.2 (300 mL), and the extracts were combined, dried over MgSO.sub.4 and concentrated. The residue. . .

DETD Phosphorothioates (P.dbd.S) are synthesized as for the phosphodiester oligonucleotides except the standard oxidation bottle was replaced by 0.2 M **solution** of 3H-1,2-benzodithiole-3-one 1,1-dioxide (Beaucage reagent) in acetonitrile for the stepwise thiation of the phosphite linkages. The thiation wait step was. . . C. (18 hr), the oligonucleotides were purified by precipitating twice with 2.5 volumes of ethanol from a 0.5 M NaCl **solution**.

DETD . . . VCAM-1. Following the appropriate incubation time with the cytokine, the cells are gently washed three times with a buffered isotonic **solution** containing calcium and magnesium such as Dulbecco's phosphate buffered saline (D-PBS). The cells are then directly fixed on the microtiter. . . albumin in D-PBS for 1 hour at 37.degree. C. Cells are incubated with the appropriate monoclonal antibody diluted in blocking **solution** for 1 hour at 37.degree. C. Unbound antibody is removed by washing the cells three times with D-PBS. Antibody bound. . . is detected by incubation with a 1:1000 dilution of biotinylated goat anti-mouse IgG (Bethesda Research Laboratories, Gaithersberg, Md.) in blocking **solution** for 1 hour at 37.degree. C. Cells are washed three times with D-PBS and then incubated with a 1:1000 dilution. . . minutes each. The amount of .beta.-galactosidase bound to the specific monoclonal antibody is determined by developing the plate in a **solution** of 3.3 mM chlorophenolred-.beta.-D-galactopyranoside, 50 mM sodium phosphate, 1.5 mM MgCl.sub.2 ; pH=7.2 for 2 to 15 minutes at 37.degree.. . .

DETD . . . by centrifugation through 0.2 .mu.m Centrex cellulose acetate filters (Schleicher and Schuell, Keene, N.H.). oligonucleotides were added as 20.times. stock **solution** to the wells and incubated for 4 hours at 37.degree. C. Medium was removed and replaced with 150 .mu.l of. . .

DETD . . . Bethesda, Md.) for 15 hours at 4.degree. C. Immune complexes were trapped by incubation with 200 .mu.l of a 50% **suspension** of protein G-Sepharose (v/v) for 2 hours at 4.degree. C., washed 5 times with lysis buffer and resolved on an. . .

DETD . . . Opti-MEM (GIBCO, Grand Island N.Y.). Cells were treated with increasing concentrations of oligonucleotide diluted in Opti-MEM

containing 10 .mu.g/ml DOTMA **solution** (Bethesda Research Labs, Bethesda Md.) for 4 hours at 37.degree. C. The medium was removed and replaced with EGM-UV (Clonetics,. . .

DETD . . . University of California at San Diego) were treated with 1 .mu.M of oligonucleotide in the presence of 20 .mu.g/ml DOTMA/DOPE **solution** for 4 hours at 37.degree. C. The medium was replaced with methionine-free medium plus 10 dialyzed fetal calf serum and. . .

DETD . . . five mice. Each mouse was anesthetized with METOFANE.TM. and a polyester sponge impregnated with 1 ml of a 20 mg/ml **solution** of carrageenan was implanted subcutaneously. Saline was administered intravenously to Group 1 at 10 ml/kg four hours prior to sponge. . .

DETD . . . microfuge tube containing 490 .mu.L of 50 uM sodium phosphate buffer (pH 7.8). The oligonucleotide mixture is then frozen in **liquid** nitrogen and transferred to a lyophilization apparatus wherein lyophilization was carried out under high vacuum, typically for 3 hours. The. . . approximately 1 mL of double-distilled H.sub.2 O, to ensure the removal of any residual, unincorporated tritium. The final

resuspended oligonucleotide **solution** is transferred to a clean polypropylene vial and assayed. The tritium labeled oligonucleotide is stored at about -70.degree. C.

DETD

Component	Mole Ratio	Mole %	mg lipid	mL stock lipid **solution**
DMPG	0.263	5	5.2	0.258
DPPC	3	57	62.7	3.137
Chol	2	38	22.0	1.102

DETD Oligonucleotide (ISIS 3082) was dissolved in water to 100 mg/mL. The **solution** was made isotonic (80-310 mOsm) with the addition of a small quantity of 5M NaCl as needed. The final **solution** was filtered through a 0.22 .mu.m membrane. Then, 0.5 mL of the resultant oligo **solution** was added to the flask containing the lipid film. The flask was rotated at 240 rpm at 60.degree. C. for 5 minutes. The lipid **suspension** was vortexed heavily to form large multi-lamellar liposomes.

DETD . . . flask into a 60.degree. C. water bath as necessary. The preceding freeze/thaw steps were repeated 5 times. The resulting liposome **solution** appeared "creamy."

DETD . . . chambers having a volume of 5.1 ml were filled with isotonic phosphate buffer (pH 7.2) containing 0.1% (v/v) of 36% **aqueous** formaldehyde as preservative. Receptor temperatures were maintained at 37.+-.0.5.degree. C. and stirred continuously at 600 rpm. The skins were allowed. . .

DETD Oligonucleotide (ISIS 2302) was added on top of the enhancer **solution**. ISIS 2302 was added to each donor compartment as a 200 .mu.l normal saline **solution** containing both 1 mg of unlabeled oligonucleotide and approximately 300,000 DPM of radiolabeled oligonucleotide. Epidermal, dermal and receptor penetration values. . .

DETD . . . and surfactants such as glyceryl monosterate, stearic acid and bees wax. Oligonucleotide was dissolved in a water phase consisting of **aqueous** surfactants and viscosity imparting agents such as polyoxyl-40 stearate and polyethylene glycol derivatives. Cream formulations consisting of water (36-45% w/w),. . .

DETD 2. ISIS 3082 **solution** at 10 mg/mL;

DETD . . . dry film of lipids in a glass container with either phosphate buffered saline at pH 7.4 or a 10 mg/mL **solution** of ISIS 3082 in PBS. The hydrated lipids were then extruded 21 times through a 50 nm membrane to form. . .

DETD . . . 2) and DMPG liposomes show about 30% to about 40% reduction in

PMA-induced ICAM-1 expression, whereas the phosphate buffered saline **solution** formulation and DPPC liposomes show less than 10% reduction. The results prove that ISIS 3082 penetrates the skin when mixed. . .

DETD . . . essentially according to the procedures of Panayiotis (Pharm. Res., 1984, 11:1385). An aliquot of 0.6 ml of ISIS 2302 stock **solution** (200 mg/ml) was transferred to a 30 ml beaker containing 1.0 ml of Tween 80 (Sigma Chemical Company St. Louis,. . . Corp., Janesville, Wis.) and 2.1 ml of Capmul MCM (Abitec Corp., Janesville, Wis.) was added to the beaker. The resultant **solution** was stirred until a clear **solution** was formed.

DETD A water-in-oil microemulsion of ISIS 2302 was prepared essentially by adding the oil phase to the **aqueous** phase with adequate mixing. The **aqueous** phase was prepared by mixing 1 ml of a 100 mg/ml **solution** of ISIS 2302 and 1 ml of Tween 80 (Sigma Chemical Company St. Louis, Mo.). The oil phase was prepared. . . Corp., Janesville, Wis.) and 1 part of Capmul MCM (Abitec Corp., Janesville, Wis.). The oil phase was added to the **aqueous** phase with adequate stirring until the resultant mixture was a clear **solution**.

DETD . . . of ISIS 2302 was prepared by first preparing the two phases. A 4 ml aliquot of the ISIS 2302 stock **solution** (100 mg/ml) was transferred to a 10 ml beaker and warmed to 70.degree. C. In a 30 ml beaker were. . . (Abitec Corp., Janesville, Wis.), and 3 ml of Labrasol (Gattefosse, France) and this mixture also warmed to 70.degree. C. The **aqueous solution** of oligonucleotide was then poured slowly into the oil phase with vigorous mixing. Upon cooling to ambient temperature the desired. . .

DETD . . . of ISIS 2302 was prepared by first preparing the two phases. A 2.3 ml aliquot of the ISIS 2302 stock **solution** (100 mg/ml) was mixed with 0.5 ml of Tween 80 (Sigma Chemical Company St. Louis, Mo.) in a 30 ml. . . Labrasol (Gattefosse, France) and this mixture also warmed to about 70.degree. C. The oil phase was then poured into the **aqueous solution** of oligonucleotide with vigorous mixing. Upon cooling to ambient temperature the desired oil-in-water cream formulation was obtained.

DETD Five formulations were evaluated. Two **solution** formulations were prepared. Formulation 1a was prepared by dissolving ISIS 2302 and a combination of CDCA and fatty acid penetration. . .

DETD TABLE 9

Absolute Bioavailability of ISIS 2302 Following Intrajejunal Instillation in Rats

Formulation	**Composition**	Absolute Bioavailability
1a	ISIS 2302 + CDCA + Fatty acids	14.6% (n = 5)
solution		
1b	ISIS 2302 + UDCA + Fatty acids	12.4% (n = 2)
solution		
1c	ISIS 2302 +	20.3% (n = 5)
emulsion	Labrasol + Captex + Grill 3	
1d	ISIS 2302 + CDCA + Fatty acids. . .	

DETD When a control **solution** of ISIS 2302 was administered no significant amount of oligonucleotides was found to be absorbed at steady state. In contrast, when ISIS 2302 was formulated as a **solution** that contained a mixture of fatty acid and bile salts (Formulations 1a and 1b) a significant amount of oligonucleotide was.

DETD . . . the delivery and mucosal penetration of oligonucleotides into the colon following rectal delivery, the following formulations were prepared (Table 10). **Solution** and emulsion formulations of ISIS 2302 were prepared. Additives used in the formulations included saline, hydroxypropyl methyl cellulose (HPMC), carrageenan, Vitamin E a-tocopheryl polyethyelene glycol 1000 succinate (**TPGS**), Tween 80 and sorbitol.

DETD Formulation 2a: A **solution** of ISIS 2302 was prepared in sterile saline at the desired concentration and used for in vivo evaluation.

DETD Formulation 2b: A **solution** of ISIS 2302 and hydroxypropyl methyl cellulose (HPMC) was prepared such that the final concentration of ISIS 2302 was identical. . .

DETD Formulation 2c: A **solution** of ISIS 2302 was prepared, as for Formulation 2a, containing 1.0% carrageenan and 2.5% Vitamin E **TPGS**.

DETD TABLE 10

ISIS 2302 Formulations Formulation	**Composition**
2a	ISIS 2302 in Saline
2b (HPMC)	ISIS 2302 + 1.5% Hydroxypropyl Methyl Cellulose
2c	ISIS 2302 + 1.0% Carrageenan + 2.5% Vitamin E a-Tocopheryl Polyethylene Glycol 1000 Succinate (**TPGS**) (Source: Eastman Chemical Company, NY)
2d	ISIS 2302 in a water-in-oil emulsion
2e	ISIS 2302 + 0.5% Tween 80 + 0.75% HPMC

2f. . .

DETD . . . of 100 mg/mL in vials filled to 1.2 mL, containing 100 mg (1.0 mL) of recoverable drug in a saline **solution**. A dosage of, e.g., 2 mg/kg) was injected under sterile conditions into 100 mL of normal saline and infused over. . .

CLM What is claimed is:

4. A pharmaceutical **composition** comprising the antisense oligonucleotide of claim 3.

5. The pharmaceutical **composition** of claim 4 further comprising one or more of the following: saline, a colloidal dispersion system, a liposome, an emulsion,. . .

6. The pharmaceutical **composition** of claim 3 comprising SEQ ID NO: 22.

10. The method of claim 9 wherein the antisense oligonucleotide is formulated in a pharmaceutical **composition** comprising one or more of the following: saline, a colloidal dispersion system, a liposome, an emulsion, a cream or a. . .

=> d his

(FILE 'HOME' ENTERED AT 16:50:22 ON 27 JUL 2001)

FILE 'REGISTRY' ENTERED AT 16:50:26 ON 27 JUL 2001

L1 1 S ETOPOSIDE/CN

L2 1 S TENIPOSIDE/CN

FILE 'CAPLUS, MEDLINE, USPATFULL' ENTERED AT 16:51:13 ON 27 JUL 2001

L3 12276 S L1

L4 1690 S L2

L5 671 S L3 AND L4

L6 572 DUP REM L5 (99 DUPLICATES REMOVED)

```
L7            58 S L6 AND (FLUID OR SOLUTION OR AQUEOUS OR SUSPENSION)
L8            42 S L7 AND CANCER
L9             0 S L8 AND TOCOFEROL
L10           42 DUP REM L8 (0 DUPLICATES REMOVED)
L11        16673 S ETOPOSIDE
L12         2380 S TENIPOSIDE
L13         1047 S L11 (P) L12
L14          608 S L13 AND (LIQUID OR FLUID OR SOLUTION OR SUSPENSION OR
AQUEOUS
L15          485 S L14 AND COMPOSITION
L16          153 S L15 AND MICELLE?
L17          153 DUP REM L16 (0 DUPLICATES REMOVED)
L18          129 S L17 AND ((OXYETHYLENE?) OR ?OXYETHYLENE OR
POLYVINLPYRROLIDON
L19            2 S L18 AND TPGS

=> s l19 and tocoferol

L20            0 L19 AND TOCOFEROL
```

STRUCTURE FILE UPDATES: 28 NOV 2000 HIGHEST RN 304849-62-5
DICTIONARY FILE UPDATES: 28 NOV 2000 HIGHEST RN 304849-62-5

TSCA INFORMATION NOW CURRENT THROUGH July 8, 2000

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Structure search limits have been increased. See HELP SLIMIT for details.

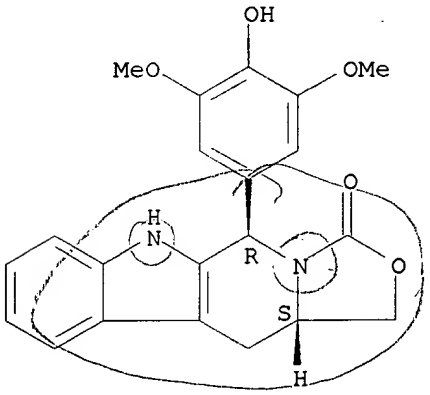
=> s azatoxin/cn

L1 1 AZATOXIN/CN

=> d l1

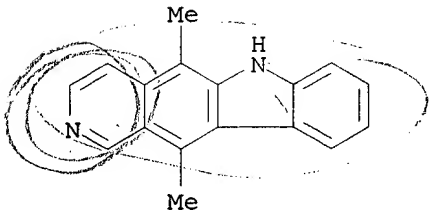
L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2000 ACS
RN 129564-92-7 REGISTRY
CN 1H,3H-Oxazolo[3',4':1,6]pyrido[3,4-b]indol-3-one, 5,6,11,11a-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-, (5R,11aS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H,3H-Oxazolo[3',4':1,6]pyrido[3,4-b]indol-3-one, 5,6,11,11a-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-, (5R-cis)-
OTHER NAMES:
CN **Azatoxin**
CN NSC 640737
FS STEREOSEARCH
DR 144262-22-6
MF C21 H20 N2 O5
SR CA
LC STN Files: ADISINSIGHT, BIOSIS, CA, CANCERLIT, CAPLUS, DRUGUPDATES, MEDLINE, PHAR, TOXLINE, TOXLIT, USPATFULL

Absolute stereochemistry.



19 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
19 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2000 ACS
RN 519-23-3 REGISTRY
CN 6H-Pyrido[4,3-b]carbazole, 5,11-dimethyl- (7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Ellipticine (6CI)**
OTHER NAMES:
CN 5,11-Dimethyl-6H-pyrido[4,3-b]carbazole
CN CP 5
CN NSC 71795
FS 3D CONCORD
MF C17 H14 N2
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CHEMLIST, CSCHEM, DDFU, DRUGU, EMBASE, IPA, MEDLINE, MRCK*, NAPRALERT, NIOSHTIC, PROMT, RTECS*, SPECINFO, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)



522 REFERENCES IN FILE CA (1967 TO DATE)
118 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
522 REFERENCES IN FILE CAPLUS (1967 TO DATE)
8 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

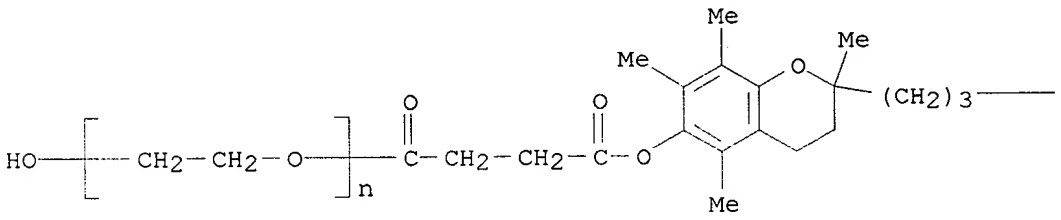
=> s tpgs/cn

L3 1 TPGS/CN

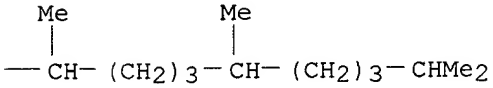
=> d l3

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2000 ACS
RN 9002-96-4 REGISTRY
CN Poly(oxy-1,2-ethanediyl), .alpha.-[4-[[(2R)-3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-2H-1-benzopyran-6-yl]oxy]-1,4-dioxobutyl]-.omega.-hydroxy- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Poly(oxy-1,2-ethanediyl), .alpha.-[4-[[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl]oxy]-1,4-dioxobutyl]-.omega.-hydroxy-, [2R-[2R*(4R*,8R*)]]-
OTHER NAMES:
CN .alpha.-Tocopherol polyethylene glycol succinate
CN .alpha.-Tocopheryl polyethylene glycol succinate
CN D 1T
CN D-.alpha.-Tocopherol polyethylene glycol 1000 succinate
CN d-.alpha.-Tocopheryl poly(ethylene glycol) 1000 succinate
CN D-.alpha.-Tocopheryl polyethylene glycol succinate
CN Tocofersolan
CN Tocophersolan
CN **TPGS**
DR 162849-98-1, 58829-13-3, 75139-00-3, 30999-06-5, 32408-94-9
MF (C2 H4 O)n C33 H54 O5
CI PMS
PCT Polyether
LC STN Files: AGRICOLA, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CEN, CHEMLIST, CIN, DDFU, DRUGU, EMBASE, IPA, MEDLINE, PROMT, RTECS*, TOXLINE, TOXLIT, USAN, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: WHO

PAGE 1-A



PAGE 1-B



75 REFERENCES IN FILE CA (1967 TO DATE)
76 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> file caplus

L33 ANSWER 1 OF 1 USPATFULL

AB Lipophilic active ingredients are co-melted with tocopherol polyethyleneglycol succinate (TPGS) and a dispersion adjuvant to obtain solid dry coprecipitate compositions suitable as an oral dosage form. The solid TPGS coprecipitates of lipophilic active ingredients show improved drug release in vitro and enhanced oral bioavailability in vivo.

AN 1999:43218 USPATFULL

TI Solid Coprecipitates for enhanced bioavailability of lipophilic substances

IN Amselem, Shimon, Rehovot, Israel

PA Pharmos Corporation, New York, NY, United States (U.S. corporation)

PI US 5891469 19990406

AI US 1997-833076 19970402 (8)

DT Utility

EXNAM Primary Examiner: Harrison, Robert H.

LREP Pennie & Edmonds LLP

CLMN Number of Claims: 22

ECL Exemplary Claim: 1

DRWN 6 Drawing Figure(s); 6 Drawing Page(s)

LN.CNT 778

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Solid Coprecipitates for enhanced bioavailability of lipophilic substances

SUMM . . . and low oral bioavailability which could benefit from oral dosage forms are the antifungal agent amphotericin B, the anticancer drug **etoposide**, as well as tamoxifen and its analogs.

SUMM . . . coprecipitate compositions are advantageous for the oral delivery of Coenzyme Q10 as a dietary nutrient supplement, melatonin, dexanabinol, amphotericin B, **etoposide**, tamoxifen quaternary amine analogs, or for any appropriate lipophilic substance.

DETD . . . bioavailability which could benefit from oral dosage forms are the neurohormone melatonin, the antifungal agent amphotericin B, the anticancer drug **etoposide**, as well as tamoxifen and its analogs. More specific compounds include cannabinoids, as exemplified by dexanabinol, and vitamins, enzymes or. . .

DETD Preparation of TPGS/PVP powdered coprecipitate of **Etoposide**

DETD TPGS (500 mg) was melted at 40.degree.-60.degree. C. in a water bath. **Etoposide** (100 mg, from Sigma, St. Louis, USA) was added to the melted material and the mixture was agitated for several. . . ml of a 5% solution in water) was added and the mixture was agitated again for several minutes. The resultant TPGS/PVP/**Etoposide** mixture was then freeze-dried overnight using a Christ beta lyophilizer (Germany). A powdered free-flowing TPGS/PVP/**Etoposide** coprecipitate quickly dispersible in water was obtained.

CLM What is claimed is:

14. The composition of claim 1 wherein the lipophilic substance is selected from the group consisting of dexanabinol, **etoposide**, coenzyme Q10, melatonin, amphotericin, tamoxifen and tamoxifen methiodide.

. . . of claim 19 wherein the coprecipitate comprises as the lipophilic substance an agent selected from the group consisting of dexanabinol, **etoposide**, coenzyme Q10, melatonin, amphotericin, tamoxifen and tamoxifen methiodide.

IT 58-95-7, .alpha.-Tocopherol acetate 73-31-4, Melatonin 1397-89-3, Amphotericin B 7631-86-9, Silica, biological studies **9002-96-4** 9003-39-8, PVP 10540-29-1, Tamoxifen 12633-72-6, Amphotericin 25322-68-3, PEG 33419-42-0, Etoposide 59865-13-3, Cyclosporin A 107256-99-5
(solid coppts. for enhanced bioavailability of lipophilic substances)

L44 ANSWER 1 OF 7 USPATFULL

AB Lipophilic active ingredients are co-melted with tocopherol polyethyleneglycol succinate (TPGS) and a dispersion adjuvant to obtain solid dry coprecipitate compositions suitable as an oral dosage form. The solid TPGS coprecipitates of lipophilic active ingredients show improved drug release in vitro and enhanced oral bioavailability in vivo.

AN 1999:43218 USPATFULL

TI Solid Coprecipitates for enhanced bioavailability of lipophilic substances

IN Amselem, Shimon, Rehovot, Israel

PA Pharmos Corporation, New York, NY, United States (U.S. corporation)

PI US 5891469 19990406

AI US 1997-833076 19970402 (8)

DT Utility

EXNAM Primary Examiner: Harrison, Robert H.

LREP Pennie & Edmonds LLP

CLMN Number of Claims: 22

ECL Exemplary Claim: 1

DRWN 6 Drawing Figure(s); 6 Drawing Page(s)

LN.CNT 778

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Solid Coprecipitates for enhanced bioavailability of lipophilic substances

DETD After mixing with body fluids, such as gastric fluid, these compositions undergo quick dissolution with resultant **micelle** formation or emulsification. A good example of a surfactant vehicle (which can quickly disperse drug coprecipitates) is alpha-tocopherol polyethylene glycol. . . hydrophobic d-alpha-tocopherol hemisuccinate (acid). TPGS is a water soluble compound (to 20% w/v) and forms micellar solutions with a critical **micelle** concentration (CMC) of 0.4-0.6 mM (about 0.075%). The hydrophilic-lipophilic balance (HLB) of TPGS is about 15-19. The amphipathic nature of. . .

CLM What is claimed is:

14. The composition of claim 1 wherein the lipophilic substance is selected from the group consisting of dexanabinol, **etoposide**, coenzyme Q10, melatonin, amphotericin, tamoxifen and tamoxifen methiodide.

. . . of claim 19 wherein the coprecipitate comprises as the lipophilic substance an agent selected from the group consisting of dexanabinol, **etoposide**, coenzyme Q10, melatonin, amphotericin, tamoxifen and tamoxifen methiodide.

L43 ANSWER 1 OF 1 USPATFULL

AB Lipophilic active ingredients are co-melted with tocopherol polyethyleneglycol succinate (TPGS) and a dispersion adjuvant to obtain solid dry coprecipitate compositions suitable as an oral dosage form. The solid TPGS coprecipitates of lipophilic active ingredients show improved drug release in vitro and enhanced oral bioavailability in vivo.

AN 1999:43218 USPATFULL

TI Solid Coprecipitates for enhanced bioavailability of lipophilic substances

IN Amselem, Shimon, Rehovot, Israel
PA Pharmos Corporation, New York, NY, United States (U.S. corporation)

PI US 5891469 19990406
AI US 1997-833076 19970402 (8)
DT Utility
EXNAM Primary Examiner: Harrison, Robert H.
LREP Pennie & Edmonds LLP
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN 6 Drawing Figure(s); 6 Drawing Page(s)
LN.CNT 778
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Solid Coprecipitates for enhanced bioavailability of lipophilic substances

CLM What is claimed is:

14. The composition of claim 1 wherein the lipophilic substance is selected from the group consisting of dexanabinol, **etoposide**, coenzyme Q10, melatonin, amphotericin, tamoxifen and tamoxifen methiodide.

. . . of claim 19 wherein the coprecipitate comprises as the lipophilic substance an agent selected from the group consisting of dexanabinol, **etoposide**, coenzyme Q10, melatonin, amphotericin, tamoxifen and tamoxifen methiodide.

IT 58-95-7, .alpha.-Tocopherol acetate 73-31-4, Melatonin 1397-89-3, Amphotericin B 7631-86-9, Silica, biological studies **9002-96-4** 9003-39-8, PVP 10540-29-1, Tamoxifen 12633-72-6, Amphotericin 25322-68-3, PEG 33419-42-0, Etoposide 59865-13-3, Cyclosporin A 107256-99-5
(solid coppts. for enhanced bioavailability of lipophilic substances)